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D3 lymph node dissection improves survival in stage IV colorectal cancer：A Propensity Score-Matched Retrospective Study

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Abstract

Background: Optimal surgical treatment of stage IV colorectal cancer (metastatic CRC [mCRC]) remains controversial. The present study was undertaken to investigate the impact of extensive lymph node dissection (LND) in this setting.

Methods: This retrospective cohort study analyzed 581 patients with stage IV CRC at a high-volume cancer center in Japan. All received surgical treatment between April 2007 and December 2020. Subjects were stratified by nature of LND (D3 vs non-D3 [nD3]) and then propensity score matched at 1:1 ratio. Overall survival (OS) and Cancer-specific survival (CSS) was analyzed before and after pairing, determining independent risk factors through COX regression.

Results: Patients assigned to D3 and nD3 LND groups totaled 389 (67.0%) and 192 (33.0%), respectively. Five-year OS proved superior for the D3 (vs nD3) group, both before (42.0% vs 17.9%; p<0.001) and after (51.0% vs 18.1%; p<0.001) PSM. Lymph Node Metastasis (LNM)also emerged as an independent prognosticator of OS in multivariate analyses conducted before (hazard ratio [HR]=0.44, 95% confidence interval [CI]: 0.34-0.57; p<0.001) and after (HR=0.36, 95% CI: 0.251-0.52; p<0.001) matching.

The same was true of 5-year CSS, both before (D3, 43.9%; nD3, 20.2%; p<0.001) and after (D3, 52.8%; nD3, 20.2%; p<0.001) matching, again verifying LNM as an independent prognostic factor before (HR=0.43, 95% CI: 0.33-0.56; p<0.001) and after (HR=0.35, 95% CI: 0.245-0.51; p<0.001) PSM. No significant differences in perioperative complications were observed between groups before or after matching.

Conclusions: D3 LND improves the prognosis of patients with stage IV CRC, without triggering undue perioperative complications.

Introduction

Despite extensive screening to detect early phases of colorectal cancer (CRC), approximately 15–20% of patients afflicted with CRC harbor synchronous distant metastases at time of diagnosis(1, 2). Regarding treatment of stage IV CRC (metastatic CRC [mCRC]), recent advances made in chemotherapy and other palliative care modalities(3–5) have failed to quell existing controversy over strategic surgical intervention(6, 7). The oncologic benefit conferred by various methods of tumor removal, including lymph node dissection (LND), is particularly unclear in instances of palliative primary tumor resection.

In Japan, the extent of LND depends on CRC staging, aiming to strike an appropriate balance between aggressive surgery and cure rate(8). Guidelines for treatment of colorectal cancer established by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) stipulate differing levels of lymph node dissection (LND) based on invasive tumor depth. Mesenteric lymph nodes are separable into pericolic, intermediate, and apical compartments. D1 LND is confined to pericolic lymph nodes, whereas D2 LND is directed at both pericolic and intermediate sectors, and the dissection of pericolic, intermediate, and

apical lymph nodes is defined as D3 LND(9). However, few studies have yet addressed the rigorousness of LND during radical treatment of mCRC.

Herein, we examined specific levels of LND to gauge the prognostic benefits achieved when performed during primary tumor resections in patients with mCRC. To our knowledge, this is the first large-scale study comparing D3 vs. non-D3 LND in stage IV CRC with propensity score matching.

Patients and methods

Scope of lymph node dissections

All tumor (T) and LND classifications adhered to guidelines of the JSCCR (7th Edition). Mesenteric lymph nodes were thus separable into pericolic, intermediate, and apical compartments, with D1 LND confined to pericolic lymph nodes, D2 LND directed at both pericolic and intermediate sectors, and D3 LND encompassing all three. A non-D3 (nD3) LND designation signaled D1 or D2 dissection level. In radical resection of right colon cancer, the boundary of the D3 LND is the left margin of the superior mesenteric vein (SMV). If the LND just reached the right edge of the SMV, it is counted as D2 LND. For radical rectal cancer resection and left-sided colectomy, to the root of the IMA, the LND exposing the abdominal aorta is defined as D3 LND, and the LND at the level of the left colonic artery only is defined as D2 LND.

Data collection and statistical analysis

This retrospective cohort study relied on data collected during a 13-year period (April 2007 to December 2020) at Saitama Medical University International Medical Center in Japan. The institution's Ethics Committee approved our investigation, and all subjects granted written informed consent preoperatively. A total of 6,234 patients submitting to surgical resections of CRC were studied. A total of 681 patients were mCRC and cases with simultaneous or metachronous resection of distant metastases were included in the study. We excluded those with unknown survival statues, unknown LND and D0 or D1 LND were also grounds for exclusion. Finally, 581 patients were eligible, each undergoing laparoscopic CRC resections plus simultaneous or stepwise resections of distant metastases. Initially, we reviewed patient backgrounds and perioperative outcomes. Propensity score matching (PSM) served to offset differences in baseline variables, and multivariate regression models were used to identify potential independent risk factors. The following parameters were incorporated into a multivariate model for PSM: sex; age; family history of cancer; history of abdominal surgery; carcinoembryonic antigen (CEA) level; postoperative complications; tumor location, size, histotype, and differentiation status; lymphatic invasion; perineural infiltration; vascular invasion; distribution of distant metastases; and pathologic T or N class.

Logistic regression analysis was also performed to determine differences in cancer-specific survival (CSS) rate by LND level (D3 vs nD3). To assess differences in categorical variables, chi-square and Fisher's exact tests were applied. Kaplan-Meier plots provided estimates of OS and CSS. All statistical

computations were driven by standard software (SPSS v22; IBM Corp, Armonk, NY, USA), To test for differences in categorical variables, chi-square and Fisher's exact tests were applied. We used Kaplan-Meier method to estimate CSS and OS, setting significance at $p < 0.05$.

Results

Among the total of 6,234 surgical patients with primary CRC, 581(9.32%) were patients with distant metastasis (mCRC). The mCRC patients were grouped as either nD3 (192, 33.0%) or D3 (389, 67.0%) LND (Fig. 1). By comparison, members of the D3 (vs nD3) LND group were younger (65.9 ± 11 vs 68.4 ± 11.8; $p = 0.014$) and more inclined to develop rectal cancers (44.7% vs 28.6%; $p < 0.001$), with familial tumor histories (59.4% vs 50.0%; $p = 0.04$) and neoadjuvant chemotherapy (46.5% vs 29.7%; $p < 0.001$) in greater proportion. Overall, the D3 LND group showed lower CEA levels (< 5 ng/mL: 31.9% vs 19.3%; $p = 0.002$) as well. The two groups did not differ in terms of sex, history of abdominal surgery, tumor size, operative blood loss, postoperative complications, or postoperative hospital stay (Table 1). We compared perioperative outcomes of the two groups. Before and after matching, there were no statistical differences with regard to operative blood loss ≥ 20 ml (before PSM: 44.78% vs 49.72% [$p = 0.234$]; after PSM: 50% vs 48.8% [$p = 0.91$]), complication rate (before PSM: 23.7% vs 26.6% [$p = 0.507$]; after PSM: 18.6% vs 23.6% [$p = 0.379$]), or length of hospital stay (before PSM: 10.4 ± 8.8 vs 11.8 ± 14 [$p = 0.148$]; after PSM: 11.6 ± 14.2 vs 9.8 ± 6.3 [$p = 0.145$]) (Table 1).

Table 1
Clinical characteristics and surgical results before and after propensity score matching (PSM)

Parameters	Before PSM			After PSM		
	nD3 LND	D3 LND	*p*-value	nD3 LND	D3 LND	*p*-value
Sex (total)	192	389		140	140	
Female	75(39.1%)	138 (35.5%)	NS	46 (40.0%)	52 (37.1%)	NS
Male	117 (60.9%)	251 (64.5%)		105 (62.5%)	103 (61.3%)	
Age (years)	68.4 ± 11.8	65.9 ± 11	0.014	67.9 ± 10.9	68.1 ± 11.6	NS
Family history of cancer						
No	96 (50%)	158 (40.6%)	0.04	55(39.3%)	64 (45.7%)	NS
Yes	96(50%)	231 (59.4%)		85(60.7%)	76 (54.3%)	
CEA (ng/ml)						
<5	37 (19.3%)	124 (31.9%)	0.002	30 (21.4%)	29(20.7%)	NS
≥5	155 (80.7%)	265 (68.1%)		110 (78.6%)	111 (79.3%)	
Tumor location						
Colon	137 (71.4%)	215 (55.3%)	< 0.001	97 (69.3%)	98 (70%)	NS
Rectum	55 (28.6%)	174 (44.7%)		43 (30.7%)	42 (30%)	
Tumor size (cm)						
<5	80 (41.7%)	136 (35%)	NS	45 (32.1%)	54 (38.6%)	NS
≥5	112 (58.3%)	253 (65%)		95 (67.9%)	86 (61.4%)	
Postoperative complications						

CEA, carcinoembryonic antigen; PSM, propensity score matching; D3 LND: D3 lymph node dissection; nD3 LND: non-D3 lymph node dissection (D1 or D2); NS, not significant.

Parameters	Before PSM			After PSM		
	nD3 LND	D3 LND	*p*-value	nD3 LND	D3 LND	*p*-value
No	141 (73.4%)	297 (76.3%)	NS	107 (76.4%)	114 (81.4%)	NS
Yes	51 (26.6%)	92 (23.7%)		33 (23.6%)	26 (18.6%)	
Postoperative hospital stay (days)	11.8 ± 14	10.4 ± 8.8	NS	9.8 ± 6.3	11.6 ± 14.2	NS
Chemotherapy						
No/unknown	135 (70.3%)	208 (53.5%)	< 0.001	91 (65%)	87 (62.1%)	NS
Yes	57 (29.7%)	181 (46.5%)		57 (40.7%)	53 (37.9%)	

CEA, carcinoembryonic antigen; PSM, propensity score matching; D3 LND: D3 lymph node dissection; nD3 LND: non-D3 lymph node dissection (D1 or D2); NS, not significant.

Within this cohort, metastases were distributed as follows: liver, 358 (53.5%); lung, 145 (21.7%); peritoneum, 101 (15.1%); distant lymph nodes, 54 (8.0%); and bone, 11 (1.64%). Postoperative pathologic examinations indicated fewer peritoneal metastasis in the D3 (vs nD3) LND group (12.6% vs 27.1%; $p < 0.001$), although other variables proved similar for each. These included tumor histotype, differentiation, signs of lymphatic or venous invasion, depth of infiltration, (T) or N class, and metastases elsewhere (liver, lung, distant lymph nodes, and bone) (Table 2).

Table 2
Pathologic characteristics of patients with stage IV CRC (mCRC) before and after propensity score matching (PSM)

Parameters	Before PSM			After PSM		
	nD3 LND (n = 192)	D3 LND (n = 389)	*p*-value	nD3 LND (n = 140)	D3 LND (n = 140)	*p*-value
Histotype						
Adenocarcinoma	175 (91.1%)	364(93.6%)	NS	132 (94.3%)	130 (92.9%)	NS
Sig/Muc	17 (8.9%)	25(6.4%)		8 (8.3%)	10 (7.1%)	
Differentiation						
Well, Mod	159 (82.8%)	339(87.1%)	NS	121 (86.4%)	121 (86.4%)	NS
Poor/Sig/Muc	33 (17.2%)	50(12.9%)		19 (13.6%)	19 (13.6%)	
T class						
T1-T2	4 (2.1%)	12 (3.1%)	NS	4 (2.9%)	3 (2.1%)	NS
T3-T4	188 (97.9%)	352 (96.9%)		136 (97.1%)	137 (97.9%)	
N class						
N0-N1	114 (59.4%)	205 (52.7%)	NS	83 (59.3%)	79 (76.4%)	NS
N2	78 (40.6%)	184 (47.3%)		85 (60.7%)	89 (63.6%)	
Lymphatic invasion						
No	70 (36.5%)	168 (43.2%)	NS	55 (39.3%)	51 (36.4%)	NS
Yes	122 (63.5%)	221 (56.8%)		106 (63.1%)	98 (58.3%)	
Venous invasion						
No	20 (10.4%)	53 (13.6%)	NS	14 (10.0%)	21 (15.0%)	NS

PSM, propensity score matching; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; Muc, mucinous carcinoma; Sig, signet ring cell carcinoma; NS, not significant; D3 LND, D3 lymph node dissection; nD3 LND, non-D3 lymph node dissection (D1 or D2)

Parameters	Before PSM			After PSM		
	nD3 LND (n = 192)	D3 LND (n = 389)	*p*-value	nD3 LND (n = 140)	D3 LND (n = 140)	*p*-value
Yes	172 (89.6%)	336 (86.4%)		126 (90.0%)	119 (85.0%)	
Liver metastasis						
No	74 (38.5%)	149 (38.3%)	NS	49 (35.3%)	50 (35.7%)	NS
Yes	118 (61.5%)	240 (61.7%)		91 (65.0%)	90 (64.3%)	
Lung metastasis						
No	147 (76.6%)	289 (74.3%)	NS	105 (75.0%)	119 (85.0%)	NS
Yes	45 (23.4%)	100 (25.7%)		35 (25.0%)	21 (15.0%)	
Peritoneal metastasis						
No	140 (72.9%)	340 (87.4%)	< 0.001	106 (75.7%)	111 (79.3%)	NS
Yes	52 (27.1%)	49 (12.6%)		34 (24.3%)	29 (20.7%)	
Distant lymph node metastasis						
No	169 (88.0%)	358 (92.0%)	NS	12 (8.6%)	14 (10.0%)	NS
Yes	23 (12.0%)	31 (8.0%)		128 (91.4%)	126 (90.0%)	
Bone metastasis						
No	188 (97.9%)	382 (98.2%)	NS	138 (98.6%)	138 (98.6%)	NS
Yes	4 (2.3%)	7 (1.8%)		2 (1.4%)	2 (1.4%)	

PSM, propensity score matching; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; Muc, mucinous carcinoma; Sig, signet ring cell carcinoma; NS, not significant; D3 LND, D3 lymph node dissection; nD3 LND, non-D3 lymph node dissection (D1 or D2)

Outcomes of LND analysis before matching

In analyzing long-term outcomes of LND subsets, the D3 (vs nD3) LND group demonstrated significantly better 5-year OS (42.0% vs 17.9%; $p < 0.001$) (Fig. 2A) and CSS (43.9% vs 20.2%; $p < 0.001$) (Fig. 3A).

Cox regression analysis was done before PSM to assess effects of various parameters on patient prognosis. D3 LND subsequently emerged as a significant independent predictor of OS (hazard ratio [HR] = 0.44, 95% confidence interval [CI]: 0.34–0.57; $p < 0.001$), as did postoperative complications (HR = 1.51, 95% CI: 1.15–1.98; $p = 0.003$), N class (HR = 1.69, 95% CI: 1.31–2.18; $p < 0.001$), liver metastasis (HR = 0.61, 95% CI: 0.43–0.86; $p = 0.005$), lung metastasis (HR = 0.57, 95% CI: 0.41–0.79; $p < 0.001$), tumor histotype (HR = 0.36, 95% CI: 0.24–0.54; $p < 0.001$), and chemotherapy (HR = 0.57, 95% CI: 0.44–0.74; $p < 0.001$) (Table 3).

Table 3
Multivariate logistic regression analysis of OS before and after propensity score matching (PSM)

Variable	OS Before PSM			OS After PSM		
	HR	HR (95% CI)	*p*-value	HR	HR (95% CI)	*p*-value
D3 LND vs nD3 LND	0.44	(0.34–0.57)	< 0.001	0.36	(0.251–0.52)	< 0.001
Colon vs rectum	0.8	(0.62–1.04)	0.094	0.5	(0.33–0.74)	0.02
Age (years)	1.08	(0.85–1.38)	0.534	1.41	(0.989–2.01)	0.058
Family history of tumor, yes vs no	1.06	(0.83–1.35)	0.638	0.89	(0.624–1.28)	0.547
Postoperative complications, yes vs no	1.51	(1.15–1.98)	0.003	1.55	(1.028–2.35)	0.036
CEA (ng/ml), < 5 vs ≥ 5	1.24	(0.94–1.63)	0.13	1.28	(0.815–2.01)	0.284
Tumor size (cm), < 5 vs ≥ 5	1.06	(0.82–1.37)	0.673	1.05	(0.7–1.56)	0.827
T class, 1–2 vs 3–4	1.94	(0.78–4.87)	0.156	3.79	(0.877–16.39)	0.074
N class, 0–1 vs 2	1.69	(1.31–2.18)	< 0.001	1.57	(1.089–2.27)	0.016
Liver metastasis, yes vs no	0.61	(0.43–0.86)	0.005	0.51	(0.294–0.89)	0.019
Lung metastasis, yes vs no	0.57	(0.41–0.79)	< 0.001	0.61	(0.385–0.98)	0.041
Differentiation, Well/Mod vs Poor/Muc/Sig	0.36	(0.24–0.54)	< 0.001	0.32	(0.173–0.57)	< 0.001
Chemotherapy, yes vs no	0.57	(0.46–0.74)	< 0.001	0.5	(0.333–0.75)	< 0.001

HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; Muc, mucinous carcinoma; Sig, signet ring cell carcinoma; D3 LND, D3 lymph node dissection; nD3 LND, non-D3 lymph node dissection (D1 or D2)

Findings were similar for 5-year CSS, D3 LND again constituting a significant independent predictor (HR = 0.43, 95% CI: 0.33–0.56; $p < 0.001$), along with postoperative complications (HR = 1.36, 95% CI: 1.03–1.80; $p = 0.032$), N class (HR = 1.64, 95% CI: 1.26–2.14; $p < 0.001$), liver metastasis (HR = 0.64, 95% CI: 0.44–0.94; $p = 0.009$), lung metastasis (HR = 0.55, 95% CI: 0.39–0.77; $p < 0.001$), tumor histotype (HR =

0.34, 95% CI: 0.22–0.51; $p < 0.001$), and chemotherapy (HR = 0.61, 95% CI: 0.46–0.79; $p < 0.001$) (Table 4).

Table 4
Multivariate logistic regression analysis of CSS before and after propensity score matching (PSM)

Variable	CSS Before PSM			CSS After PSM		
	HR	HR (95% CI)	*p*-value	HR	HR (95% CI)	*p*-value
D3 LND vs nD3 LND	0.43	(0.33–0.56)	< 0.001	0.35	(0.245–0.51)	< 0.001
Colon vs rectum	0.8	(0.62–1.05)	0.108	0.5	(0.33–0.76)	0.101
Age (years)	1	(0.78–1.29)	0.982	1.36	(0.947–1.95)	0.096
Family history of tumor, yes vs no	1.06	(0.82–1.36)	0.651	0.86	(0.593–1.24)	0.411
Postoperative complications, yes vs no	1.36	(1.03–1.80)	0.032	1.48	(0.97–2.26)	0.069
CEA (ng/ml), < 5 vs ≥ 5	1.24	(0.94–1.65)	0.13	1.26	(0.798–1.99)	0.322
Tumor size (cm), < 5 vs ≥ 5	1.04	(0.79–1.36)	0.78	1.07	(0.711–1.61)	0.741
T class, 1–2 vs 3–4	1.8	(0.71–4.51)	0.213	3.53	(0.814–15.35)	0.092
N class, 0–1 vs 2	1.64	(1.26–2.14)	< 0.001	1.55	(1.065–2.25)	0.022
Liver metastasis, yes vs no	0.64	(0.44–0.94)	0.009	0.51	(0.29–0.9)	0.02
Lung metastasis, yes vs no	0.55	(0.39–0.77)	< 0.001	0.61	(0.379–0.98)	0.042
Histology, ade vs muc or sig	0.87	(0.50–1.50)	0.608	1.25	(0.556–2.83)	0.584
Differentiation, Well/Mod vs Poor/Muc/Sig	0.34	(0.22–0.51)	< 0.001	0.3	(0.161–0.54)	< 0.001
Chemotherapy, yes vs no	0.61	(0.46–0.79)	< 0.001	0.54	(0.356–0.81)	0.003

HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; Muc, mucinous carcinoma; Sig, signet ring cell carcinoma; D3 LND, D3 lymph node dissection; nD3 LND, non-D3 lymph node dissection (D1 or D2)

Outcomes of LND analysis after matching

After 1:1 PSM (D3, 140; nD3, 140), we compared clinical characteristics and pathologic variables of LND subsets. Univariate analysis confirmed that the two groups were comparable (Table 1), and OS was still better in the D3 (vs nD3) LND group (51.0% vs 18.1%; $p < 0.001$) (Fig. 2B). D3 LND (HR = 0.36, 95% CI: 0.251–0.52; $p < 0.001$) also proved to be independently predictive of OS, in addition to postoperative complications(HR = 1.55, 95% CI: 1.028–2.35; $p = 0.036$), N class (HR = 1.57, 95% CI: 1.089–2.27; $p = 0.016$), liver metastasis (HR = 0.51, 95% CI: 0.294–0.89; $p = 0.019$), lung metastasis (HR = 0.61, 95% CI: 0.385–0.98; $p = 0.041$), tumor histotype (HR = 0.32, 95% CI: 0.173–0.51; $p < 0.001$), and chemotherapy (HR = 0.5, 95% CI: 0.333–0.75; $p < 0.001$) (Table 3).

Likewise, the D3 LND group surpassed the nD3 LND group in CSS (52.8% vs 20.2%; $p < 0.001$) (Fig. 3B), and LND was identified as a significant independent predictor of CSS (HR = 0.35, CI:0.245–0.51; $p < 0.001$). Other factors predictive of CSS included N class (HR = 1.55, 95% CI: 1.065–2.25; $p = 0.022$), liver metastasis (HR = 0.51, 95% CI: 0.29–0.90; $p = 0.02$), lung metastasis (HR = 0.61, 95% CI: 0.379–0.98; $p = 0.042$), tumor histotype (HR = 0.3, 95% CI: 0.161–0.54; $p < 0.001$), and chemotherapy (HR = 0.54, 95% CI: 0.356–0.81; $p = 0.003$) (Table 4).

Finally, we studied the metastatic distribution of mCRC. Among the total of 6,234 CRC patients, 3,691(59.2%) patients were colon cancer. 2,543(40.8%) patients were rectal cancer. Liver metastasis occurred in 358(5.73%) patients, lung metastasis in 145 (2.32%) patients, distant lymph node metastasis in 54 (0.86%) patients, peritoneal metastasis in 101(1.61%) patients, and bone metastasis in 11 (0.17%) patients (Table 5).

Table 5
The frequency of simultaneous distant metastasis of colorectal cancer (CRC)

	Liver	Lung	Distant lymph node	Peritoneum	Bone
Total CRC	5.73%	2.32%	0.86%	1.61%	0.17%
n = 6234	358	145	54	101	11
Colon	6.23%	1.86%	0.92%	1.97%	0.13%
n = 3691	230	69	34	73	5
Rectal	5.03%	2.98%	0.78%	1.10%	0.23%
n = 2543	128	76	20	28	6

Discussion

Our study demonstrates that D3 LND prolongs cancer-specific survival (CSS) and serves as an independent prognostic factor for CSS in mCRC. Japanese guidelines for treatment of CRC base decisions to resect primary lesions of mCRC on the tumor classifications in question(9). In actual

practice, however, surgeons who suspect metastasis of CRC may seriously doubt that radical D3 LND will truly alter the prognosis. Our data provides evidence to the contrary, underscoring the benefit of D3 LND in the treatment of advanced disease.

The standard surgical approach to CRC in Western countries is complete mesocolic excision with central venous ligation (CME/CVL)(10, 11), whereas D3 LND is additionally performed in Japan. Degrees of longitudinal resection and numbers of harvested lymph nodes may vary, but both strategies embody analogous principles and do provide good oncologic outcomes(12). The most fundamental difference between D3 and nD3 LNDs is the rather diminished scope of root lymph node dissection and corresponding resected area of mesentery entailed in nD3 LND. For patients with mCRC, CME/CVL procedures may eradicate primary lesions sufficiently to effect overall reductions in minor tumor metastasis(13).

Several factors are already known to influence the prognosis of mCRC (14, 15). Certain studies have confirmed that patients with *KRAS* gene mutations may not derive much benefit from even primary resection(16) and that left-sided CRC is less ominous than a right-sided counterpart(17). Our data now underscores the prognostic implications of D3 LND, postoperative complications, extent of lymph node metastasis, degree of tumor differentiation, and adjuvant chemotherapy for mCRC.

In treatment of peritoneal metastases by mCRC, the utility of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy remains inconclusive(18, 19). Radical resection of primary tumors is currently advocated in Japan for patients with P1 or P2 peritoneal metastasis, and doing so may help improve patient prognosis(20, 21).

Why can D3 LND improve the prognosis of mCRC? Firstly, D3LND may reduce the tumor burden, completely clear the pericolic, intermediate, and apical lymph nodes, and lower the risk of local recurrence. Even if there is distant metastasis, the reduction of tumor burden in the primary lesion area may delay systemic progression. D3LND can dissect the apical lymph nodes, and accurately determine the pN stage, which can guide the intensity of postoperative chemotherapy such as the Folinic Acid (Leucovorin), Fluorouracil, Oxaliplatin and Irinotecan (FOLFOXRI) intensive regimen and the selection of targeted drugs. For patients with oligometastatic liver/lung metastases (≤ 3), the combined resection of the primary lesion D3LND and the metastatic lesion can achieve "cytoreductive surgery" to further clear the tumor burden in the body.

Of course, surgical strategies are ultimately dictated by baseline patient conditions. Members of our nD3 (vs D3) LND group were relatively older and more often had histories of abdominal surgery. In patients at risk of abdominal adhesions, D3 LND may pose a greater challenge. One frequent dilemma in elderly patients is weighing the scope of surgery against disease prognosis. There are concerns that sweeping resections may be fraught with adversity. Patients with stage IV CRC are consequently at high risk of postoperative complications. Nonetheless, we saw no significant group-wise differences in durations of hospitalization or rates of postoperative complications during this investigation. Hence, D3 LND offers a seemingly viable means of prolonging CSS, without undermining hospital stays or patient safety.

Certain limitations of the above study must be acknowledged, the first being its single-center retrospective design. Distant metastases were also resected (simultaneously or stepwise) or were controlled by radiochemotherapy. Unfortunately, the related accounts were not always clear, potentially introducing bias. Finally, our sample population was relatively small, perhaps impacting the results. Further consideration and validation are therefore warranted in a larger series of patients with synchronous distant mCRC.

Conclusion

D3 LND improves the prognosis of patients with stage IV CRC, without triggering undue perioperative complications.

Declarations

Author contributions

Liming Wang and Haoyue Ma provided original pictures and drafted the manuscript, which was reviewed by Yinggang Chen and Yasumitsu Hirano. All authors have approved the final submission.

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Availability of data and materials

Not applicable

Ethics approval and consent to participate

All the study participants provided their informed consent. The study design was approved by the Ethics Committee of the Saitama Medical University International Medical Center.

Consent for publication

All patients have agreed to use their personal medical data for research and publication.

Conflicts of interest

The authors have no competing interests to declare in relation to this study.

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Figures

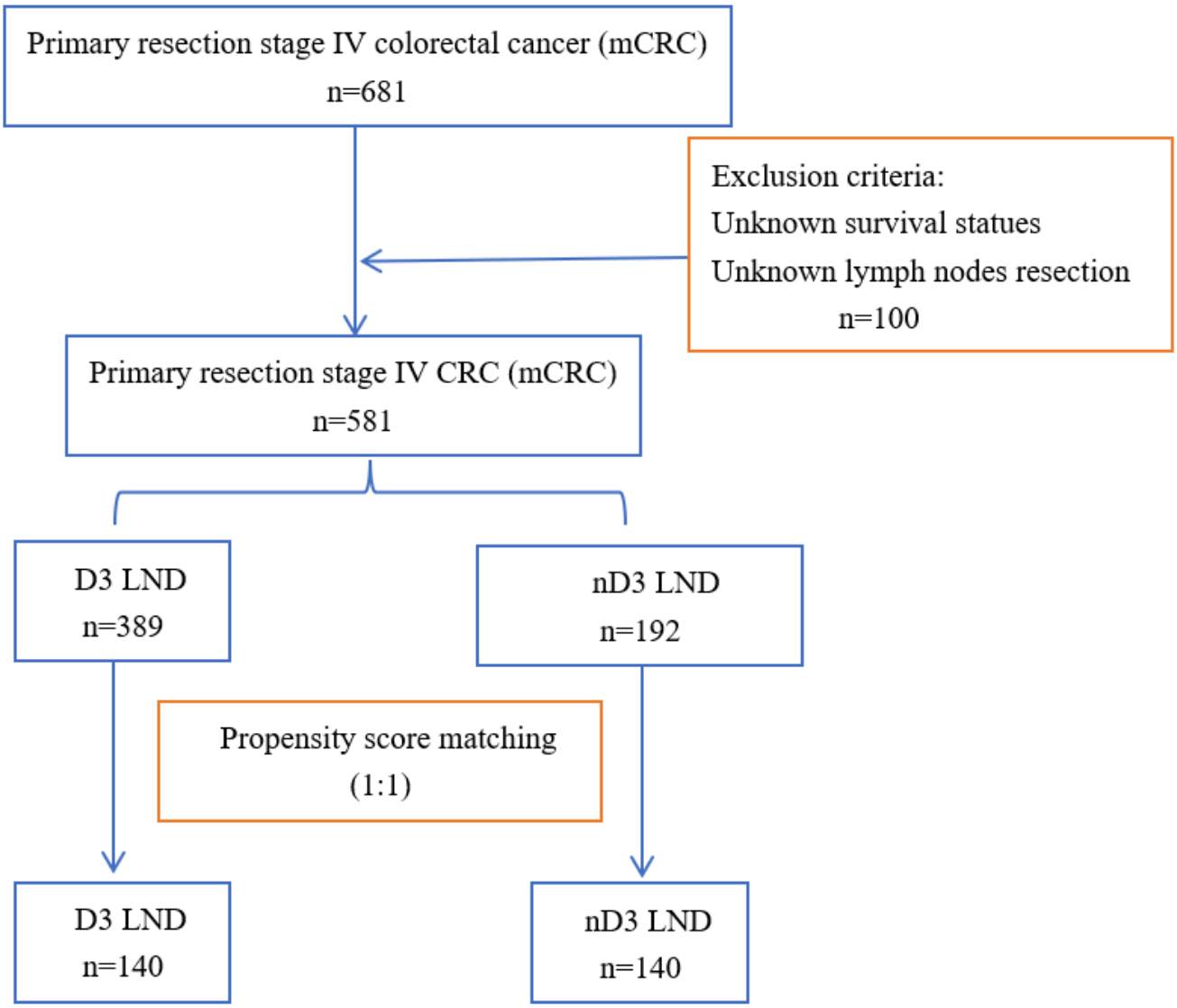

Figure 1

Schematic of patient allocation/study design

CRC, colorectal cancer; mCRC, metastatic CRC; D3 LND, D3 lymph node dissection; nD3 LND, non-D3 lymph node dissection (D1 or D2)

Figure 2A

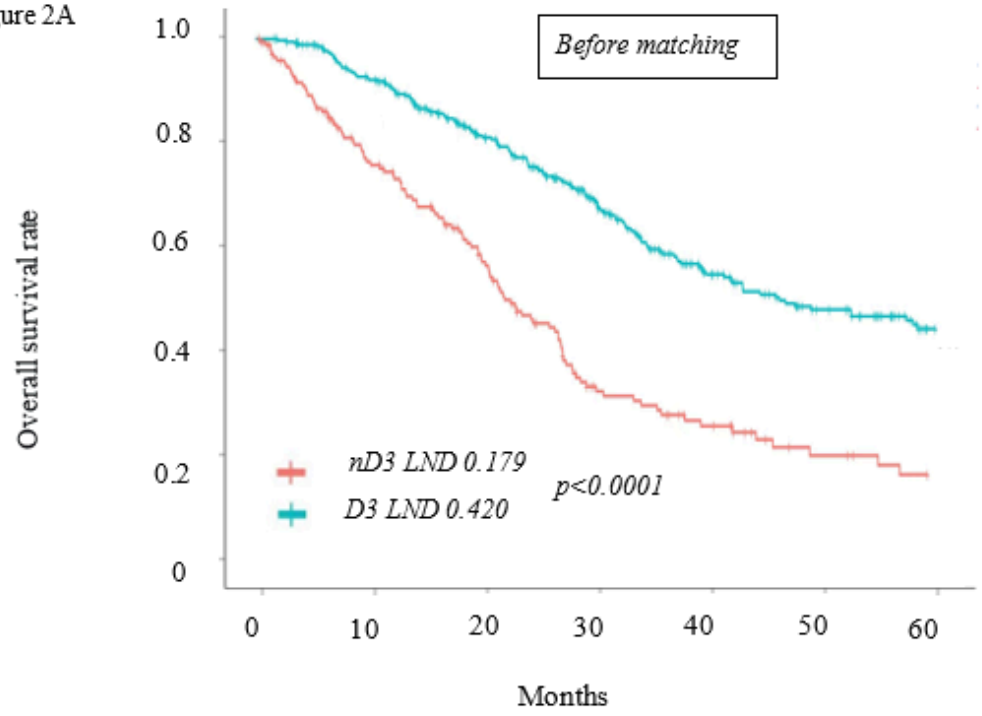

Figure 2B

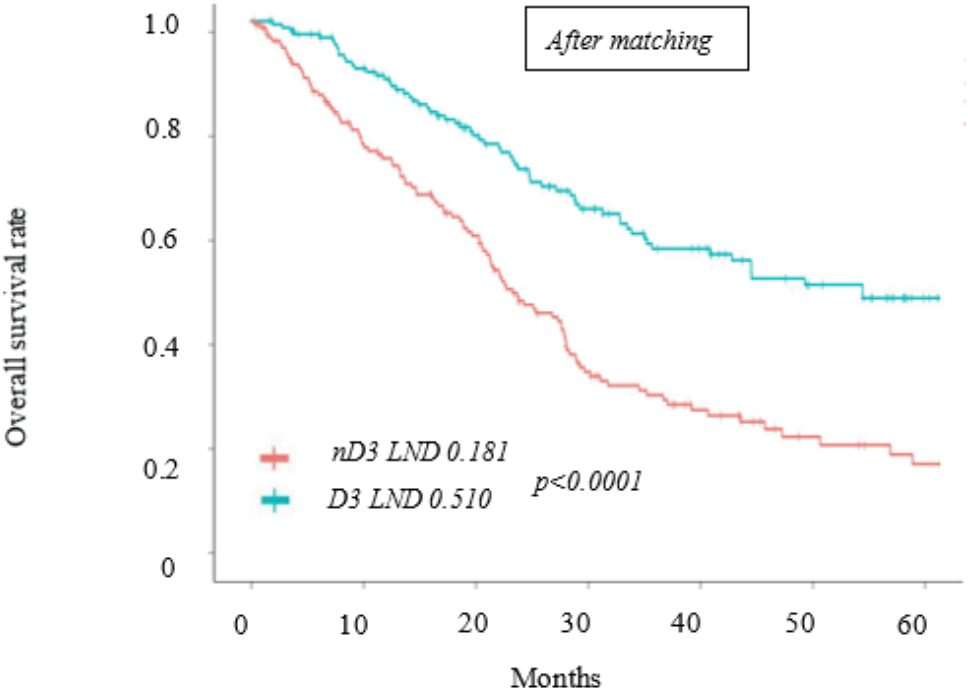

Figure 2

Overall survival (OS) rates in patients with stage IV colorectal cancer (mCRC) analyzed before (2A) and after (2B) propensity score matching

Figure 3A

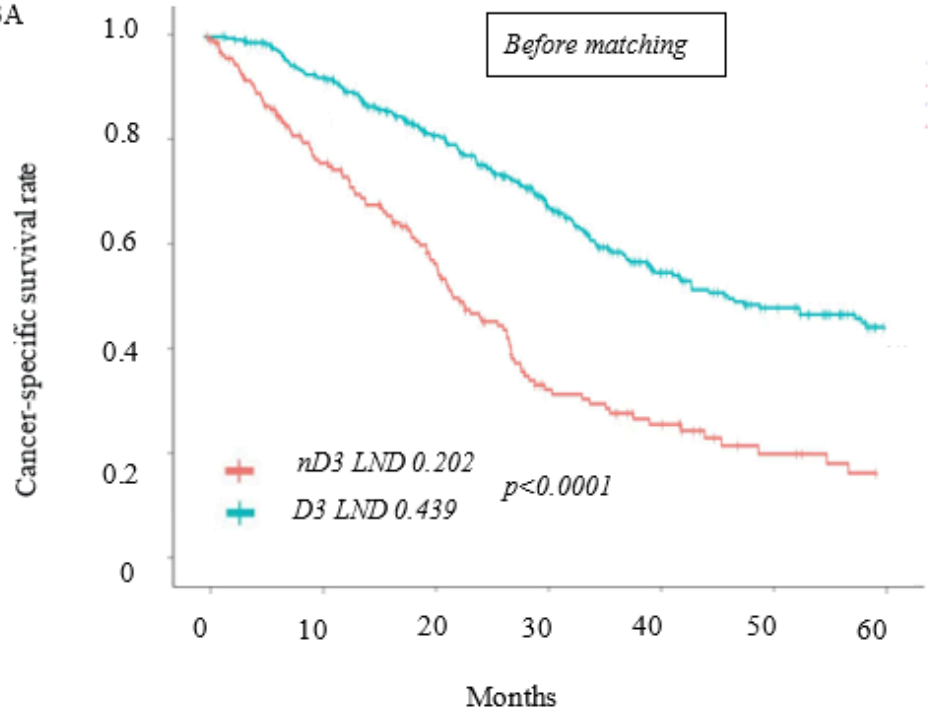

Figure 3B

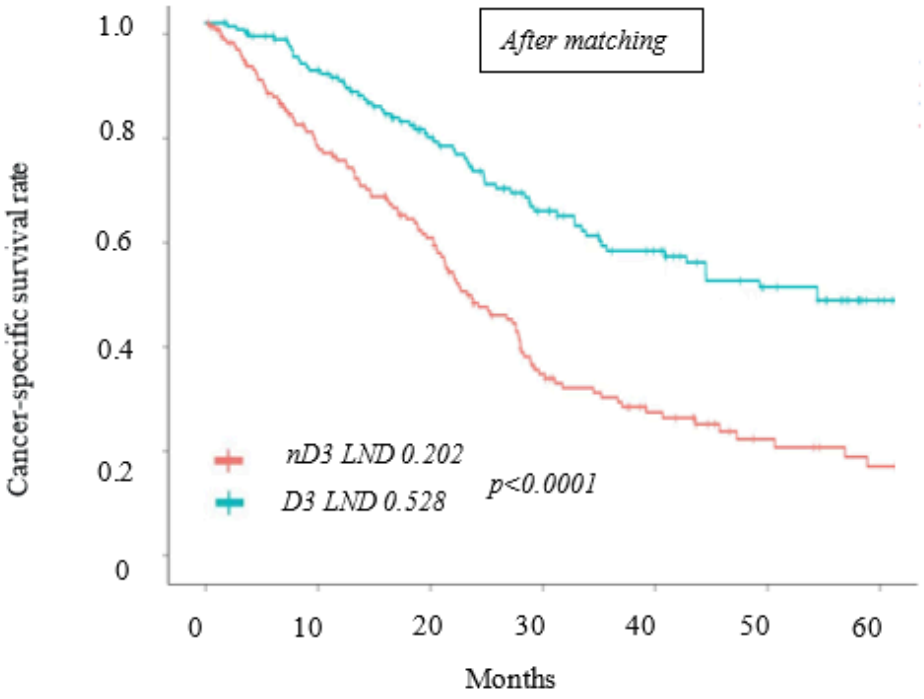

Figure 3

Cancer-specific survival (CSS) rates in patients with stage IV colorectal cancer (mCRC) analyzed before (3A) and after (3B) propensity score matching